



Role for targeted resection in the multidisciplinary treatment of metastatic gastrointestinal stromal tumor

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Abstract: The management of advanced gastrointestinal stromal tumors (GISTs) has evolved in the modern era due to the discovery of *c-kit* mutations and the development of tyrosine kinase inhibitors (TKIs). Until the advent of TKIs such as imatinib, the median survival reported for patients with advanced GIST was 19 months. Although surgery is the treatment of choice for resectable primary GIST, its role in cases of recurrence and metastasis remains to be unclear. This review outlines the potential beneficial role of repeat surgical resection in the multidisciplinary treatment of advanced GIST in the era of TKIs.

Keywords: *KIT*; *PDGFR*; resection

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Introduction

Gastrointestinal stromal tumors (GISTs) are neoplasms derived from the pacemaker cells of the gut-termed cells of Cajal. As a result, they can develop anywhere along the gastrointestinal (GI) tract, and they are the most common sarcoma and mesenchymal neoplasm of the GI tract.

The management of advanced GIST has evolved in the modern era due to the discovery of *c-kit* mutations and the development of tyrosine kinase inhibitors (TKIs). Until the advent of TKIs such as imatinib, the median survival reported for patients with advanced GIST was 19 months (1,2). Although surgery is the treatment of choice for resectable primary GIST, its role in cases of recurrence and metastasis remains to be unclear.

The following is a review of the literature for the role of surgical resection in the multidisciplinary treatment of advanced GIST in the era of TKIs.

Pre-TKI Era

Prior to the development of TKIs, surgical resection was the primary treatment for localized GIST. However,

even in patients with resectable disease, the prognosis was unfavorable, as 5-year survival was only 54% (1,3). Furthermore, between 40% and 70% would develop recurrent or metastatic disease, with the median time from resection to recurrence being 2.4 years. Recurrence overwhelmingly occurs in the peritoneum, the liver, or both (3). Resection for recurrent disease was associated with a median survival of 15 months (4). While multiple chemotherapy agents had been trialed, none had any significant effect, as response rates were <10% (5). Resection of recurrent disease had mixed results. Resection of liver only recurrence was associated with 1- and 3-year survivals of 90% and 58%, respectively (6). Resection of metastatic disease resulted in a modest survival improvement with median survival being 27 months (1).

Post-TKI era

Prognosis for patients diagnosed with GIST changed radically in 2002 with the approval of imatinib mesylate by the FDA as a treatment option. The landmark study by Demetri *et al.* showed the efficacy of imatinib to produce a

sustained objective response for unresectable and metastatic GIST translating to 24-month progression free survival (PFS) and 57-month overall survival (OS) (7). These results were confirmed by the B2222 trial. These two studies have established TKI therapy as the first line treatment of unresectable and metastatic GIST.

Cytoreduction surgery following a positive response to TKI therapy was then shown to further improve survival. Fiore *et al.* demonstrated neoadjuvant TKI therapy to result in a 34% reduction in tumor size and 77% 3-year PFS in patients with unresectable or metastatic GIST (8). In another study performed by Blesius *et al.*, 60% of patients with locally advanced GIST had a positive response to TKI therapy and those patients who then underwent resection had improved PFS and OS compared to those who continued with only TKI therapy (9). The PFS and OS benefits of cytoreductive surgery after a positive response to TKIs have been demonstrated in multiple additional studies (10-13).

Two studies have specifically looked at the role for cytoreductive surgery of metastatic or recurrent GIST prior to TKI therapy. In a retrospective study of 249 patients by An *et al.*, there was no improvement of PFS when comparing cytoreductive surgery followed by TKI *vs.* TKI alone (13). Change *et al.* observed an improvement in 1-, 3-, and 5-year PFS in patients undergoing cytoreductive surgery followed by TKI therapy compared to TKI therapy alone; however, this did not translate into any significant improvement in OS (14).

Intolerance of TKI therapy

While TKIs are generally well tolerated, they are not without potential adverse effects. Most adverse effects are non-life threatening: nausea, vomiting, diarrhea, muscle cramps, fatigue, hypothyroidism and fluid retention can be typically managed with ancillary treatment. However, while serious adverse effects, such as leukopenia and cardiotoxicity, can often be managed, occasionally they are severe enough to require dose reductions or cessation of treatment (15-17).

Development of TKI resistance

GIST resistance to TKIs develops in two patterns: primary and secondary. Primary resistance is defined as evidence of progression during the first 6 months of TKI therapy and is primarily seen in patients with wild-type GISTs that lack

the *KIT* or *PDGFR* mutations. Secondary resistance is seen in patients who have been on TKI therapy for 6 months with an initial response or disease stabilization, which is then followed by progression. This resistance pattern is due to the outgrowth of tumor clones with secondary mutations in *KIT* (18-21).

As far as time on therapy before surgery, the NCCN quotes the EORTC trial, which demonstrated a median time to secondary resistance of 2 years. They recommend discussing surgery around 6–12 months of disease stability or response. Finally, NCCN recommends continuation of imatinib therapy post-operatively based on a study by Rutkowski *et al.* that showed recurrent disease in patients who did not restart therapy.

Indications

There are several retrospective studies examining the role for surgical resection after imatinib therapy (13,22-28); these revealed a higher complete resection rate and improved PFS and OS after surgery in patients who responded to TKI therapy versus those who were resistant. One of the most recent and largest studies by Fairweather *et al.* reported a 14-year experience [2001–2014] from 2 institutions that identified radiographic response to TKI at time of surgery significantly influenced PFS. A similar outcome for the influence of radiographic response at time of surgery was observed in median OS from date of surgical resection (stable disease 110 months, unifocal progressive disease 59 months, and multifocal progressive disease 26 months, $P < 0.001$). Additionally, metastatic mitotic index $\geq 5/50$ HPF, presence of multifocal progressive disease, and R2 resection were all associated with worse PFS and OS.

Two randomized controlled trials have been designed examined cytoreductive surgery in combination with imatinib (neoadjuvant therapy + surgery + adjuvant therapy with imatinib) *vs.* imatinib alone. The surgery arm outperformed imatinib alone in 1- and 3-year OS (100% *vs.* 89% and 85% *vs.* 60%, respectively, $P = 0.03$) (29). Of note, this trial had a small sample size. The second randomized controlled trial conducted by Du *et al.* examined if cytoreductive surgery for imatinib responsive recurrent or metastatic GIST was superior to imatinib treatment alone. Unfortunately, this trial was closed early due to poor accrual, and there was no statistically significant difference in 2-year PFS between the surgery arm and imatinib only arm (88.4% *vs.* 57.7%, $P = 0.089$) (30).

Prediction of effective surgery

Several studies have showed tumor responsiveness to imatinib before surgery to be associated with improved OS or PFS (13,22–24,26,31). Further studies have demonstrated surgery to have limited benefit in patients with focal progressive disease (22,26), while some show improved outcomes of patients with focally progressive GISTs resistant to TKI (32,33).

A recent meta-analysis of nine studies included a total of 1,416 GIST patients, 351 received surgery. This analysis demonstrated that improved outcomes were associated with surgery and TKI in combination *vs.* TKI treatment alone in terms of OS (HR by random-effects model =0.68; 95% CI, 0.54–0.85; I^2 =48.9%) and PFS (HR =0.50; 95% CI, 0.33–0.76; P <0.05; I^2 =17.9%; P =0.296) with metastatic or recurrent GISTs. The same report, conducted a sub-analysis on OS among the two randomized controlled trials previously mentioned; however, there was no significant difference in OS among the RCT group.

To specifically look at liver metastasis, being the most common site of metastasis, Brudvik *et al.* (34) compared survival data in patients with GIST *vs.* leiomyosarcomas and other sarcomas. They found a 5-year recurrence free survival rate of 35.7% for GIST (49 total GIST patients) with a median time to recurrence of 17.8 months. The liver was found to be the most common area of recurrence with a rate of 41% amongst those with recurrences. Importantly, their subgroup analysis showed GIST patients had a higher recurrence free survival rate at 5 years with imatinib *vs.* those who had surgical resection alone (47.1% *vs.* 9.5%; P =0.013).

As for OS in their study, the 10-year OS was 52.5%. In a subgroup analysis they found that after resection of liver metastases from GIST, age greater than 55 years (HR =2.798; P =0.027) was associated with reduced OS, male sex (HR =0.447; P =0.071) exhibited a trend towards increased OS, and concomitant RFA (HR =2.179; P =0.085) and R1 resection (HR =4.100; P =0.066) exhibited trends toward reduced OS.

What requires further exploration is the question: who are the best candidates for surgical resection in metastatic and recurrent disease? One study performed by Roland *et al.* (35) looked to describe pre-operative characteristics that would predict favorable outcomes with surgical resection after imatinib therapy. They looked at 87 patients with metastatic or recurrent GIST who underwent preoperative TKI therapy as well as surgical resection.

The median duration of neoadjuvant TKI therapy was 667 days and 91% of patients continued TKI therapy post-operatively. At a median follow-up of 51 months from surgical resection for recurrent or metastatic GIST (91 months for survivors), the median OS was 64.5 months (95% CI, 39.2–90.9) with a median time to recurrence of 21.3 months (95% CI, 12.7–29.2). Median disease-specific survival (DSS) was 73.5 months (95% CI, 39.9–97.7) from surgical resection. Median DSS from the time of initiation of TKI therapy was 119 months (95% CI, 72.2–142.4).

In univariate analysis for pre-operative risk factors they found that unifocal disease at time of resection, duration of TKI therapy less than 365 days, and no evidence of radiographic progression were associated with improved time to recurrence and DSS. Additionally, on multivariate analysis, patients with evidence of radiographic tumor progression prior to surgical resection had a significantly worse GIST-specific survival (HR =2.53; 95% CI, 1.27–5.06; P =0.008) and increased risk of recurrence (HR =3.33; 95% CI, 1.91–5.82; P <0.001) compared to those with preoperative radiographic stable disease or regression. Patients with multifocal disease in single or multiple cavities also decreased GIST-specific survival (HR =2.61; 95% CI, 1.12–6.06; P =0.027) compared to patients with unifocal disease.

In patients whose disease has been stable on TKI therapy who develop isolated progression due to TKI-resistant clones, targeted resection may improve survival by reverting the metastatic GIST patient to a TKI-induced indolent state (13). Thus, surveillance with a history and physical exam and CT or MRI should be performed to identify those who may benefit from further resection (36).

Conclusions

Surgery for metastatic GIST should generally be performed after 6–12 months of TKI therapy, prior to development of secondary resistance, or sooner in the case of progressive disease. Cyto-reductive therapy improves PFS and OS relative to TKI therapy alone, especially in patients with advantageous biology. After resection, TKI therapy should be continued indefinitely. Initially, surveillance with history and physical exams as well as CT or MRI should be performed every 3–6 months. Further surgery for resectable disease or isolated progression can be pursued to remove TKI-resistant clones and revert the GIST to a TKI-induced indolent state.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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